From: Erik Janus
To: Rostker, David; Beck, Nancy; wooge.william@epa.gov;
cc: Becker, Rick; Kate Willett; Kristie Sullivan; Susan Ferenc; Susan Little; Beth Law; Chad Sandusky; Doug Fratz; scott slaughter;
Subject: EPA"s reponse to peer review of the ER binding assay for your information
Date: Tuesday, July 21, 2009 12:28:47 PM
Attachments: er-ruc_response_to_comments.pdf

David, Nancy -

In case you had not seen the EPA response to the rat cytosol ER binding assay peer review report, I've attached it for your consideration as you continue to interact with EPA regarding the EDSP ICR review. The story from Risk Policy Report (pasted in below) points out some rather serious shortcomings that remain. (Pay particular attention to the comments of Patrick Balaguer and Marie-Louise Scippo, as found below)

Additionally, I am told by Angela Hofmann of EPA that their contractor survey of labs potentially offering "endocrine testing services" will be due back and publically available by the end of August. My understanding is this will cover a mix of both large and small labs and will contain information both on COST but also on LAB CAPACITY, which as you know could be a serious bottleneck for certain "newer" assays where existing EPA data cannot satisfy the demands of the Tier 1 EDSP screen. I think this information could be critical to the OMB efforts to gain clarity on the issue of EDSP testing cost and capacity.

Many thanks for considering this information,
- Erik Janus

EPA VALIDATES LAST ASSAY IN ENDOCRINE SCREEN, QUESTIONS REMAIN

EPA has announced the validation of the final assay in its long-delayed endocrine disruption screening program
(EDSP), but industry and activists are already criticizing the test for failing to adequately measure the chemicals'
effects.

Industry argues the assay will produce too many false positives, overstating the risks of chemicals run through
the screen, while a source with the Endocrine Disruption Exchange (TEDX) argues that EPA should have included a
different assay in the screen.

Congress, through the Food Quality Protection Act of 1996, mandated EPA create the EDSP to screen for and determine chemicals' potential for disrupting human hormones. The assay is the last in the EDSP's first tier of assays to be validated, a key concern when EPA last year sent the program for White House review before the estrogenreceptor binding assay was validated. Industry argued last fall that the EDSP could not begin without the estrogenreceptor binding assay, described "by many as a keystone to this process," the president of pesticide industry association CropLife America said at the time (Risk Policy Report, Oct. 14).

But in comments the chemical industry association American Chemistry Council (ACC) sent the agency in March, the group raised concerns about the validation process and what ACC considered "high variability" between labs testing the assay for EPA. ACC also raised concerns about the "[p]roposed use of expert judgment in lieu of a quantitative standard for interpreting a positive, which was necessitated by the high variability" and the "[i]nsufficient number of truly negative results." Relevant documents are available on InsideEPA.com. See page 2 for details.

The EDSP is designed to screen for endocrine-disrupting chemicals in two tiers. The first is intended to detect if a chemical is capable of interacting with the estrogen, androgen or thyroid hormone systems. A chemical flagged in tier one will undergo tier-two testing, which is designed to provide data for hazard assessment. Industry and animal rights groups have for some time raised concerns that assays in the first tier will yield too many false positives, requiring more chemicals than necessary to undergo tier two tests that are more expensive and use more lab animals.

In a report concluding that the assay is validated following review by an independent panel of experts, EPA acknowledges that "[t]he criteria used for classifying a chemical as interactive or not err on the side of classifying a chemical as interactive, which is appropriate for a screening assay. Since additional assays will be used in Tier 1 screening before a final determination of the potential for interaction is assigned, and additional Tier 2 assays will be

performed to confirm the interaction and provide dose-response information before risk is assessed, the bias towards false positives is appropriate."

EPA continues, "Despite the bias towards false positives, chemicals that truly do not interact in any way with the estrogen receptor . . . consistently test negative in this assay."

The agency charged the peer review panel to determine whether the assay "is biologically and toxicologically related to its stated purpose" - which the five-member panel found to be true. But several of the experts also raised concerns about complications that could make the assay more difficult to interpret, leading one reviewer, Ingemar Pongratz of Sweden's Karolinska Institute, to conclude the assay is "only partially" related to the purpose of determining if a chemical would disrupt estrogen hormones.

The reviewers also noted that results varied between labs testing the assay, with reviewer Patrick Balaguer of the French National Institute for Health and Medical Research concluding that "the assay is sensitive to many details of preparation and technique and can show wide variability if not performed exactly as stated in the protocol."

Reviewer Marie-Louise Scippo, a professor at the University of Liège, Belgium, concluded that the assay's "main weakness comes from the use of animals to prepare the binding fraction, with not only ethical, but technical consequences (lack of reproducibility of receptor preparations.)"

A source with TEDX noted the reviewers' concerns, and argued that EPA should have used a different assay, known as the MCF7 assay, instead of the estrogen-receptor assay included. The MCF7 assay could have been validated more quickly due to its longstanding use in many labs around the world, the source says.

"I will continue to wonder if the last 13 years were not a waste of time when the MCF7 assay could have been adapted and validated early on as the estrogen screen," the source says.

An EPA spokesman points to advice the agency received from an expert panel regarding EDSP design. The committee's August 1998 report noted that tests such as the MCF7 using human

cells "are rapidly being developed
and offer both advantages and disadvantages over the above assay, one advantage being the use of the human rather
than the rat [estrogen receptor]. However, being relative[ly] new, they have not been standardized in their examination
of xenoestrogens."

The source argues that the MCF7 test, which has not gone through the same validation process that EPA's
estrogen receptor test recently completed, is preferable because of some of the exact concerns industry and the
reviewers raised. According to the source, the MCF7 does not indicate false positives, it is simple to perform, and
because it is based on an existing line of human cells, it does not require the use of lab animals. - Maria Hegstad

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